The Applicants do not intend by these or any other amendments to abandon the subject matter of any claim as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

III. The Rejection Under 35 U.S.C. § 112, First Paragraph, Is Moot

In paragraph 1 of the Official action, the Examiner objected to the specification and rejected claims 11 and 14 under 35 U.S.C. § 112, first paragraph, alleging that both the specification and claims failed to provide adequate written description and an enabling disclosure that the deposited biological material is readily available.

At the outset, the Applicants dispute the basis for rejection. As acknowledged by the Examiner, the specification does indeed provide a description of the invention and how to make and use it. Still, the applicants have provided herein a copy of the Official Receipt of the Original Deposit on Mouse hybridoma YU1 (Ferm BP-6343) issued by the National Institute of Bioscience and Human-Technology, which is an agency of the Agency of Industrial Science and Technology, which is acting as International Depository Authority under the Budapest Treaty. In addition, a signed declaration by Dr. Kazautake Tsujikawa (one of the inventors), as required by the Budapest Treaty and 37 C.F.R. § 1.808, is attached in Appendix C. The declaration attests to the deposit of the Mouse hybridoma YU1 (Ferm BP-6343).

The declaration addresses the examiner's concerns that the biological materials are deposited and readily available according to the requirements under 37 C.F.R. § 1.808. Therefore, the rejections under 35 U.S.C. § 112, first paragraph, are moot and should be withdrawn.

IV. The Rejection Under 35 U.S.C. §112, First and Second Paragraphs, Is Moot

Based on the recitation of the term "fragment" in claims 4 and 6, the Examiner rejected claims 4 and 6 under 35 U.S.C. § 112, first and second paragraphs, as containing subject matter assertedly not enabled by the specification and as containing indefinite terminology. [Official Action, paragraphs 2 through 7]. The Applicants respectfully traverse.

The Applicants dispute the rejection because one of skill in the art has no difficulty in determining whether or not a peptide is a fragment of the polypeptide recited in claims 4 and 6. Likewise, the application enables one of ordinary skill in the art to use fragments to make antibodies of the invention.

Claims 4 and 6 depend from claim 1, which reads "an antibody having specificity to a LAR phosphatase subunit." Solely to expedite prosecution, the Applicants have amended claims 4 and 6 by removing the word "fragment." The amendments do not materially limit to claims in that they affect only dependent claims. Moreover, antibodies generated against a LAR fragment that show specificity for a LAR phosphatase subunit are still within the scope of the claims. In light of the foregoing amendments, the rejections of pending claims 4 and 6 under 35 U.S.C. § 112, first and second paragraphs, are moot. The Applicants do not intend by these or any other amendments to abandon the subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

V. The Rejection Under 35 U.S.C. § 102(b) Should be Withdrawn

In paragraphs 9 and 10 of the Official action, the Examiner rejected claims 1, 4-6, 12, 13, 15, 19, 27, and 28 alleging that these claims were anticipated under 35 U.S.C. § 102(b) by Streuli *et al.*, *Embo Journal* **11**:897-907 (1992) (hereafter Streuli *et al.*, (1992)). The Examiner outlines three main points for support of her anticipation rejection, which the Applicants address in turn.

First, the Examiner alleges Streuli *et al.*, (1992) teaches that antibodies were generated using a fusion (LAR-LCA) protein to screen for antibodies specific for the LAR phosphatase subunit. Actually, Streuli *et al.*, (1992) did not disclose that the fusion protein, LAR-LCA, was used to screen for antibodies specific for the LAR phosphatase subunit. In fact, on page 898, columns 1, lines 41 and 42, and column 2, lines 1 through 5, Streuli *et al.* (1992) disclosed that the fusion protein, LAR-LCA, was used to screen for antibodies specific for the **LAR Ig domain epitopes** only (an extracellular domain of LAR's E-subunit, 150 kDa). There is no mention of isolating antibodies specific for LAR phosphatase subunits. The Applicants use a completely different fusion protein (GST-LAR) as an immunogen to screen and produce antibodies specific to the intracellular phosphatase domains of LAR (P-subunit; 85 kDa).

Second, the Examiner alleges Streuli et al., (1992) teaches monoclonal antibodies to the 85 kDa portion of LAR (designated the LAR-P subunit), which contains the intracellular PTPase domains. In actuality, all of the LAR specific antibodies listed in Streuli *et al.*, (1992) are only against the various extracelluar domains of LAR. For example, in figure 1 (page 898) of Streuli *et al.*, (1992), anti-LCA antibodies (GAP8.3 and UCHL-1), anti-LAR antibodies (38.1B, 75.3A and 108.4A), and anti-LAR antibodies (11.1A, 71.2E, 128.4A and 136.1) are targeted against CD45 extracellular domains, Ig domains of LAR, and fibronectin domains of LAR, respectively. Each of these targeted areas are located in the extracellular region of LAR (E-subunit, 150 kDa).

Streuli *et al.*, (1992) (pages 900 and 901) reports that the 85 kDa portion of LAR was immunoprecipitated. However, the immunoprecipitation was not due to any antibody directed against the 85 kDa portion of LAR. Instead, Streuli *et al.*, (1992) comments that "the association of the 150 kDa and 85 kDa subunits is sufficiently strong to resist disruption during vigorous washing of the immunoprecipitates." [Steuli *et al.*, (1992) page 900, column 2, lines 5-7.] In other words, the antibodies reported in Streuli *et al.* (1992) (as discussed above) were targeted against the 150 kDa extracellular domain of LAR; the 85 kDa protein band was only "immunoprecipitated" due to the strong association between the 150 kDa and 85 kDa subunits, which was subsequently separated by SDS-PAGE analysis. One skilled in the art who analyzed Streuli *et al.* (1992) would not interpret the article as disclosing any antibodies with immunospecifity for epitopes of the 85 kDa subunit in general, or the antigen specifically recited in the present claims.

The Applicants are presently claiming anti-LAR antibodies against intracellular regions, such as the LAR phosphatase subunit (P-subunit, 87 kDa). Therefore, Streuli, *et al.*, (1992) does not teach Applicants claimed antibodies.

The third point of the Examiner's rejection relates to claims 27 and 28, which are directed to the anti-LAR monoclonal antibody having specific immunoreactivity to thyroid carcinoma cells. With respect to these claims, the Patent Office alleges the following:

> It is inherent that the antibodies may be encoded by a polypeptide or fragment of SEQ ID NO: 1, and immunoreact with thyroid cancer cells, as Streuli, *et al.*, set forth loss of heterozygosity in the LAR gene of patients with medullary thyroid carcinoma (pg. 905).

The Applicants respectfully traverse.

As the Examiner has acknowledged, the passage at page 905, right column, lines 25-31 of Streuli *et al.*, (1992) simply noted the absence of heterozygosity in the 1p32-35 chromosomal region in patients with phaeochromocytoma and medullary thyroid carcinoma. Streuli *et al.*(1992) did not discuss the loss of heterozygosity in the LAR gene and admits it remains to be seen whether a mutation in the LAR gene is associated with any malignancy such as medullary thyroid carcinoma. In contrast, the Applicants demonstrate a selective reactivity of the anti-intracellular LAR antibody YU1 to cancerous thyroid tissue cells without any cross reactivity with normal thyroid follicular cells or stroma of tumor tissue. [See Example 5 *with emphasis* on page 47, lines 15-18; Example 6, page 49, lines 1-3; and all of Example 7] Accordingly, any effect to be offered by the antibodies in claims 27 and 28 are not demonstrated in Streuli *et al.* (1992).

Contrary to the suggestion of the Examiner, Streuli *et al.*'s antibodies do not inherently meet the specificity limitations of claims 27 and 28 regarding specific immunoreactivity with thyroid carcinoma cells. Streuli *et al.* (1992) in figure 6 at page 603 teaches that the anti-LAR 11.1 antibody (directed against the fibronectin extracellular domain of LAR) bound to normal thyroid tissue cells. In stark contrast to the antibodies that are immunoreactive to thyroid carcinoma cells in claims 27 and 28 (See Example 5 *with emphasis* on page 47, lines 15-18; Example 6, page 49, lines 1-3; and all of Example 7), the antibodies used in Streuli *et al.* fail to exhibit the ability to identify cancerous thyroid cancer cells from normal thyroid cells.

For these reasons, Streuli *et al.*, (1992) fail to teach every element set forth in claims 1, 4-6, 12, 13, 15, 19, 27, 28 and the rejection under 35 U.S.C. § 102(b) may be withdrawn.

VI. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

In paragraph 12 of the Official action, the Examiner rejected claims 1-10, 12, 13, 15-19, 27, and 28 under 35 U.S.C. § 103(a) for being directed to subject matter allegedly rendered obvious in light of the disclosures of Streuli, *et al.*, *J. Exp. Med.* **168**:1523-1529 (1988) (hereafter Streuli, *et al.* (1988)), Streuli *et al.*, *Embo Journal* 9:2399-2407 (1990) (hereafter Streuli *et al.* (1990)), and Streuli *et al.*, (1992) in view of Furukawa *et al.*, *Proc. Natl. Acad. Sci.* **91**:10928-10932 (1994) (hereafter Furukawa *et al.*). Applicants respectfully traverse.

At the outset, the Applicants respectfully wish to clarify certain factual issues raised by the Examiner's obviousness rejection. First, as explained above, even though the 85 kD portion of LAR was reported to have been "immunoprecipated" on page 900-901 of Streuli *et al.*, (1992), the immunoprecipitation was not due to antibodies specific to the intracellular region of LAR. Second, the rejection is factually incorrect in that Streuli *et al.* (1992) does not teach a correlation between the loss of heterozygosity in the LAR gene of patients with medullary thyroid carcinoma, as discussed above. Finally, the Examiner alleges Furukawa *et al.* teach antibodies to GST-LAR fusion proteins. This statement is incorrect because nowhere within the Furukawa *et al.* reference are antibodies generated against GST-LAR fusion proteins. Rather, the only antibodies used in immunoblot experiments were an anti-phosphotyrosine antibody (4G10), a GST-CD45-PTPase antibody, an antibody directed against a serine mutant of GST-CD45-PTPase, and a goat anti-CD3ζ polyclonal antibody (CT-5). None of these antibodies are directed against the LAR PTPase domains.

To establish a *prima facie* case of obviousness, at least three basic criteria must be met. First, the prior art must teach or suggest all of the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Finally, there must be a reasonable expectation of success. [*In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).] None of those criteria is satisfied here.

A. Streuli *et al* (1988, 1990, 1992) do not teach all of Applicants' claim limitations

The Streuli *et al* references do not teach or suggest all the claim limitations of the Applicants' invention. The rejected claims relate to an antibody having specificity to a LAR phosphatase subunit and the methods for generating such an antibody (P-subunit of LAR). Streuli *et al* (1988, 1990, 1992) teaches antibodies directed to the CD45 extracellular domains, Ig domains of LAR and the fibronectin domains of LAR. All of these respected domains are located in the E-subunit of LAR, which is the extracellular portion LAR. The antibody disclosed in Streuli *et al* will not bind the PTPase intracellular domains of the P-subunit of LAR, and the cited references are silent with regard to this limitation in the rejected claims i.e., an antibody having specificity to a LAR phophatase subunit. Therefore, Steuli et al., (1988, 1990, 1992) fail to teach or suggest any antibodies specific for the intracellular P-subunit of LAR.

B. The cited references do not motivate one of skill in the art to modify the referenced teachings.

In paragraph 17 of the Official action, the Examiner asserts that the Streuli *et al.* references disclose the polypeptide encoded by the Applicants' SEQ ID NO: 1 (Streuli *et al.*, (1988)) and the Applicants' antibodies specific to LAR, so that one of skill in the art could combine these teachings with Furukawa *et al.*'s disclosure of GST-LAR fusion proteins, to produce the antibody as claimed. The Examiner also asserts that one of skill in the art would have been motivated to make an antibody specific to the intracellular domain of LAR, because PTPases regulate cell proliferation and the phosphatase activity site (Streuli *et al.*, (1990)) is located in the intracytoplasmic PTPase domain (P-subunit-85kDa Streuli *et al.*, (1992)) of LTR. Furthermore, one of skill would be motivated to make an antibody not specific for CD45 in order to avoid T- and B-cell activation (Furukawa, *et al.*). Finally, one would be motivated to generate the antibody of claims 10, 12, 13, and 15-18 using the protocols taught by Streuli *et al.*, with the GST-LAR fusion protein as disclosed by Furukawa *et al.* The Examiner alleges combination of these references establishes motivation to combine the cited references. The Applicants respectfully disagree.

Contrary to what has been asserted by the Patent Office, the cited art actually taught away from the present invention and would have dissuaded one of skill in the art from attempting to make antibodies specific to the LAR intracellular domain. When comparing sequence homology between the LAR and LCA (CD45) domains, the LAR, LCA (CD45) extracellular domains indicate low sequence homology, but their respective intracellular domains demonstrate high sequence homology. Because of such structural varieties in the extracellular domain, in order to get isolate LAR-specific antibodies, skilled artisans at that time would have preferred to prepare antibodies against the extracellular domains of LAR. For example, in Streuli *et al.*, 1992, the investigators specifically used monoclonal antibodies against the extracellular domains of LAR in order to study the expression of the receptor-linked protein tyrosine phophatase LAR via proteolytic cleavage and shedding of the CAM-like extracellular regions during cell growth. [See figures 1 and 5 and page 903, second column, for example] As explained in the present application on page 6, lines 10-20, monoclonal antibodies against the P-subunit have been ignored and the cited art provided no motivation to make them. Accordingly, the worker of ordinary skill in the art would not have been motivated to combine the above cited references to generate monoclonal

antibodies to the intracellular domain of LAR, because this worker would not have had a reason to use such antibodies.

Furukawa *et al.* do not remedy these deficiencies in the Streuli *et al.* references. As discussed above, Furukawa *et al.* neither teach or suggest using antibodies against GST-LAR fusion proteins. Therefore, there is no motivation to modify Streuli *et al* with Furukawa *et al.*, because Steuli *et al.*, (1992) already taught LAR-specific antibodies, and there was no prior art motivation in Furukawa *et al.* or elsewhere to attempt to make new LAR-specific antibodies to the intracellular domains of LAR. Therefore, the above cited references fail to provide a motivation to one of skill in the art to modify the above cited references.

C. The references fail to provide an expectation of success

The third prong for establishing a *prima facie* case of obviousness also fails. In paragraph 17 of the Official action, the Examiner suggests that one would be motivated to make an antibody without specificity to CD45 and there would have been a reasonable expectation of success for making such an antibody. Applicants respectfully disagree. As discussed above, Streuli *et al.* teaches that the LAR intracellular region and the LCA intracellular regions are highly homologous regions. Based upon this teaching, antibodies designed to bind to the LAR intracellular region might bind to LCA intracellular regions. Streuli *et al.* and Furukawa *et al.* create uncertainty over the plausibility of designing antibodies to the LAR intracellular regions due to the suggestion of cross reactivity between the LAR and LCA intracellular regions, and teach a different approach (extracellular antibodies) as a solution. Therefore, Streuli *et al.* and Furukawa *et al.* provide no expectation of success to one of skill in the art.

D. Unexpected Results

Finally, the Applicants are claiming a set of antibodies with the unexpected property of distinguishing cancerous thyroid tissue cells from normal thyroid tissues cells. [See Example 5 with emphasis on page 47, lines 15-18; Example 6, page 49, lines 1-3; and all of Example 7] Streuli *et al.* (1992) in figure 6 at page 603 teaches that anti-LAR 11.1 antibody (directed against the fibronectin extracellular domain of LAR) bound to normal thyroid tissue cells and thus Streuli *et al.* (1992) fail to exhibit the ability to identify cancerous thyroid

cancer cells from normal thyroid cells. Thus, the Applicants' invention has unexpected properties that are not obvious in light of the above cited references.

E. Summary

The Applicants submit that the disclosures of Streuli *et al* (1988, 1990, 1992) in view of Furukawa *et al.* cannot render obvious any of the presently claimed subject matter due to a failure to teach all of the claim limitations, provide motivation to combine the references, or provide the worker of skill an expectation of success. In addition, the Applicants' invention has the unexpected property of acting as a marker for thyroid and other cancerous cell lines. Therefore, the Applicants submit the rejection under 35 U.S.C. § 103 should be withdrawn.

SUMMARY

In view of the remarks made herein, the Applicants believe claims 1-19, 27, and 28 are in condition for allowance and request notification of the same. Moreover, for the reasons outlined in their response to the restriction requirement, the Applicants believe the unity of the invention continues to exist and urge rejoinder of the withdrawn claims.

Respectfully submitted,

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APPENDIX A

Version with markings to show changes made

4. (Twice Amended) The antibody according to claim 1, which is generated using a polypeptide encoded by a base sequence set out in SEQ ID NO: 1 [or a fragment of said polypeptide] as an antigen.

6. (Twice Amended) The antibody according to claim 1 wherein the antibody is generated using a fusion protein comprising a LAR phosphatase domain and another protein [or a polypeptide fragment] as an immunogen.

APPENDIX B

Pending claims upon entry of the foregoing amendment

1. An antibody having specificity to a LAR phosphatase subunit.

2. An antibody having specificity to an intracellular domain of a LAR phosphatase subunit.

3. An antibody having specificity to an intracellular domain of a LAR phosphatase subunit, and having no specificity to CD45.

4. (Twice Amended) The antibody according to claim 1, which is generated using a polypeptide encoded by a base sequence set out in SEQ ID NO: 1 as an antigen.

5. (Amended) The antibody according to claim 1 wherein the antibody is a monoclonal antibody.

6. (Twice Amended) The antibody according to claim 1 wherein the antibody is generated using a fusion protein comprising a LAR phosphatase domain and another protein as an immunogen.

7. (Amended) The antibody according to claim 1 wherein the antibody is generated using a GST-LAR phosphatase domain fusion protein as an immunogen.

8. The antibody according to claim 7 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing *Escherichia coli* transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

9. The antibody according to claim 8 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione wherein the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

10. (Amended) The antibody according to claim 6 wherein the antibody that was generated using the fusion protein as an immunogen is screened using said fusion protein.

11. A monoclonal antibody having specificity to a LAR phosphatase subunit, which is produced by a hybridoma with Accession No. FERM BP-6343.

12. (Amended) The antibody according to claim 5 having a molecular weight of about 150 kDa.

13. (Amended) A hybridoma cell line that produces the antibody according to claim 5.

14. A hybridoma cell line with Accession No. FERM BP-6343.

15. (Amended) A method for generating an antibody having specificity to a LAR phosphatase subunit, comprising a step of: immunizing an animal with a fusion protein comprising a LAR phosphatase domain and another protein or polypeptide fragment.

16. (Amended) A method for generating an antibody having specificity to a LAR phosphatase subunit, comprising a step of: immunizing an animal with a GST-LAR phosphatase domain fusion protein.

17. The method according to claim 16 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing Escherichia coli transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

18. The method according to claim 17 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione wherein the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

19. (Amended) The method according to claim 15, further comprising a step of: screening antibodies generated in the immunizing step using said fusion protein to identify an antibody having specificity to a LAR phosphatase subunit.

20. (Amended) A method of quantitative determination of LAR and/or LAR derived molecule comprising the step of: determining an amount of LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain, which is contained in a test sample using the antibody according to claim 1.

21. The method according to claim 20 wherein the antibody is used in any of immunobloting, immunoprecipitation and ELISA.

22. (Amended) A method for quantitative determination of LAR and/or LAR derived molecules comprising the steps of: isolating LAR and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain, from a test sample using the antibody according to claim 1; and measuring an activity of the isolated LAR and/or LAR derived molecules.

23. The method according to claim 22 wherein affinity chromatography and/or immunoprecipitation by using a support that was bound with the antibody are utilized in the isolation step.

24. (Amended) A method for producing LAR and/or LAR derived molecules comprising the step of: isolating LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain using the antibody according to claim 1.

25. The method according to claim 24 wherein affinity chromatography and/or immunoprecipitation by using a support that was bound with the antibody are utilized in the isolation step.

26. (Amended) A method for identifying the presence of LAR and/or LAR derived molecules within tissue comprising the steps of: performing immunohistological examination using the antibody according to claim 1 to detect LAR protein and/or a fragment or a polypeptide that comprises at least a LAR intracellular domain.

27. An anti-LAR antibody having specific immunoreactivity to thyroid carcinoma cells.

28. (Amended) The antibody according to claim 1 having specific immunoreactivity to thyroid carcinoma cells.

29. (Amended) A method for diagnosis of thyroid carcinoma comprising the steps of: taking a thyroid tissue specimen from a subject suspected as suffering from thyroid cancer; and conducting diagnosis of thyroid cancer through evaluating immunoreactivity between the antibody according to claim 27 and said tissue specimen.

30. The method according to claim 29, wherein the thyroid tissue specimen is a specimen that is taken by fine needle aspiration, and the immunoreactivity is evaluated by an immunoassay.

31. The method according to claim 29 wherein the thyroid tissue specimen is a thyroid tissue section, and the immunoreactivity is evaluated by histological stainging.

32. (Amended) A composition for histological diagnosis of thyroid carcinoma comprising the antibody to claim 27.

33. (Amended) A DDS formulation that was targeted to thyroid carcinoma cells using the antibody according to claim 27.

34. The DDS formulation according to claim 33 comprising one or more materials which are selected from the group consisting of nucleic acid, iodine, radioactive iodine, technetium and a protein.

35. (Amended) The DDS formulation according to claim 33 which is a pharmaceutical composition for diagnosis of thyroid carcinoma.

36. (Amended) The DDS formulation according to claim 33 which is a pharmaceutical composition for therapy of thyroid carcinoma.

37. The DDS formulation according to claim 36 further comprising an anticancer agent.

38. (Amended) The DDS formulation according to claim 36 wherein the nucleic acid is an antisense nucleic acid or a ribozyme.

39. (Twice Amended) A method for diagnosis of thyroid carcinoma comprising the steps: measuring an expression level of LAR mRNA from thyroid tissue of a subject suspected of suffering from a thyroid carcinoma, and diagnosing the presence or absence of thyroid carcinoma from the expression level of LAR mRNA.